## REMARKS

Upon entry of the present amendments, claims 1-3, 7, 11-14, 20-22, 32-35, 38, 42, 43, 57, and 58 will be pending. Claims 4-6, 8-10, 15-19, 23-31, 36, 37, 39-41, and 44-56, have been canceled. Applicants have amended claims 1, 7, 20, 32, and 38. Support for the amendments can be found throughout the specification, and in particular, in the Examples, in which virus-free chickens and mice were used for testing (e.g., prior to infection by an influenza virus). Applicants have added new claims 57 and 58, which recite that the promoter is a cytomegalovirus promoter, e.g., as described in numerous of the Examples in the application as filed. No new matter has been added.

### Information Disclosure Statement

Applicants thank the Office for considering the references disclosed in the IDS filed October 31, 2007.

### Priority

According to the Office, this application claims the benefit of priority from U.S. Pat. Application 07/855,562 filed on March 23, 1992. However, also according to the Office, "... the parent, US-PAT 5,643,578, does not have benefit of (1) SIV antigen, (2) rotavirus antigen, (3) microsphere encapsulation of DNA, (4) methods of immunization comprising combinations of influenza antigens. Therefore these limitations will be given the benefit of US-PAT 6,841,381, filed on 27 January 1994" (at page 3). Applicants have amended the claims to cancel any reference to these features, and thus all pending claims have priority from the March 23, 1992 filing date.

### Withdrawn Rejections

Applicants note with appreciation that the Office has withdrawn (Office Action at pages 4-6) various rejections under 35 U.S.C. § 112, first and second paragraphs. Thus, only double

patenting and obviousness rejections remain. We will first address the obviousness-type double patenting rejection.

Obviousness-Type Double Patenting

The Office alleges (at pages 12 to 16) that most or all of the pending claims are unpatentable over claims 1 to 16 of U.S. Patent No. 6,165,993, over claims 1 to 27 of U.S. Patent No. 6,187,319, and over claims 1 to 19 of U.S. Patent No. 5,643,578. Applicants traverse for the following reasons.

First, with respect to U.S. Patent Nos. 6,165,993 and 6,187,319, both of these patents claim methods of producing an immune response against a rotavirus infection. Without acquiescing to the Office's assertions and without prejudice to pursuing such claims in future applications, applicants have canceled all reference to rotavirus in the present claims. Thus, this double patenting rejection should be withdrawn with respect to these two patents.

Second, with respect to U.S. Patent No. 5,643,578, applicants refer the Examiner to the Terminal Disclaimer filed by applicants in this application on September 14, 2007. This Disclaimer applies to the present application and disclaimed a terminal portion of any patent that issues from the present application subsequent to the expiration of U.S. Patent No. 5,643,578. Thus, the present double patenting rejection should be withdrawn.

35 U.S.C. § 103

The Office rejected claims 1-4, 6-8, 11-23, 25-27, 30-35, 37-39, 42-43, 52-56 as allegedly obvious over Felgner et al. (WO90/11092; "Felgner") in view of Huylebroeck et al. (Gene, June 1988, 66(2): 163-81; "Huylebroeck"), Townsend et al. (Cell, November 1984, 39(1): 13-25), Atkinson et al. (U.S. Pat. No. 4,861,864; "Atkinson"), and Andrianov et al. (U.S. Pat. No.5,529,777; "Andrianov"). Applicants traverse this rejection for the following reasons and in view of the claim amendments, which clarify that the vertebrate is administered the recited compositions, prior to infection by an influenza virus.

The Office Action repeats at pages 9-11 text from the prior Action:

> Felgner et al. teach plasmid vectors comprising "therapeutic polynucleotides ... [which] code for immunity-conferring polypeptides, which act as endogenous immunogens to provoke a humoral or cellular response, or both"...
>
> Huylebroeck et al. teach plasmid DNA mediated gene transfer of two different influenza A antigens, including H1 hemagglutinin (abstract) ...
>
> Townsend et al. teach plasmids comprising hemagglutinin antigens ...
>
> Atkinson et al. teach a plasmid comprising cDNA of a rotavirus antigen for expression of VP7 ...
>
> Andrianov et al. teach "polymeric hydrogels are used to encapsulate antigen to form vaccines ... microparticles are formed ....preferred polymers are alginate" (abstract) and "enhanced immunogenicity of microspheres formed of 95% alginate" ...
>
> Regarding the rationale for combining prior art elements according to known methods to yield predictable results, all of the claimed elements were known in the prior art and one skilled in the art could have combined the element as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

To this argument, the Office has added in the latest Office Action, the suggestion that "Felgner et al. teach, 'Normal vaccination schemes will always produce a humoral immune response....The humoral system protects a vaccinated individual from subsequent challenge from a pathogen'" (at page 7). However, the Office has taken this excerpt from Felgner out of context. In fact, these sentences from Felgner refer to known prior art polypeptide vaccination schemes. The sentences cited by the Examiner are in a paragraph that begins: "Vaccination has changed little since the time of Louis Pasteur (at page 3, lines 12-13). Thus, the phrases quoted from Felgner by the Examiner do not refer to Felgner's ideas relating to polynucleotide vaccinations, and certainly do not describe anything that Felgner actually demonstrated.

The Office has already conceded that Felgner does not teach specific antigens for influenza virus, and repeats that admission at page 9 of the present Office Action. The Office also repeats (at page 10) the admission that none of Huylebroeck, Townsend, or Atkinson describes DNA vaccines. Instead, the Office alleges that because plasmids encoding an influenza virus antigen were generally known, and because Felgner suggests the general concept

of DNA vaccines, it would have been predictable that direct administration of these plasmids to a subject would successfully immunize the subject against a subsequent infection. Applicants disagree for the following reasons.

Applicants submit that none of the references, individually or combined, suggest that a DNA vaccine could be used **successfully** to *protect a subject from a subsequent viral infection.* Thus, even assuming that skilled practitioners would have been led to combine the teachings of these references, the instant claims would not have been obvious, as there would have been no expectation of success, much less a reasonable expectation of success, at the time of the present invention. In fact, applicants submit that the entire field of polynucleotide vaccination was highly unpredictable at the time of the present invention (before the present priority date of March 23, 1992).

In contrast, the present specification demonstrates in several different animal models (chickens, mice, and ferrets) that applicants were successful in providing actual protective immunization via multiple different routes of administration (e.g., intramuscular, intravenous, intraperitoneal, subcutaneous, intradermal, and intranasal; see, e.g., Examples 1 to 9) against a subsequent influenza infection. As stated in the specification (at page 7, lines 9-11), "...a vertebrate immunized by the present invention will not be infected or will be infected to a lesser extent than would occur without immunization." In other words, applicants' plasmid vectors did not merely induce antibody responses or treat existing infections. Rather, the induced protective immune responses protected immunized animals against subsequent challenges with otherwise lethal doses of influenza virus.

Before discussing Felgner further, applicants remind the Examiner of the meaning of the phrase "protective immune response" as recited in the claims. A protective immune response is an immune response, e.g., a humoral immune response or a cell-mediated immune response induced by an antigen, that protects (partially or totally) an immunized subject from subsequent infection by an infectious agent. This type of *prophylactic* response is very different from a *therapeutic* treatment of an existing viral infection, and is not at all obvious from such a therapeutic treatment. To help clarify the presently claimed invention, applicants amended the

remaining independent claims 1 and 32 to indicate that the recited compositions are administered to the vertebrate prior to infection by an influenza virus. This concept is clear from the specification and is exemplified in the examples, in which pathogen-free chickens and BALB/C mice were used in the tests.

While Felgner generally discloses the introduction of DNA or RNA into vertebrates for a variety of applications, including so-called immunization, applicants have found no actual data in Felgner to suggest that DNA vaccines can be used to successfully immunize a subject against infection from an influenza virus, or any virus for that matter.

Whatever data Felgner discloses regarding DNA immunization are limited to HIV, and none of the data demonstrate that any DNA vaccine can confer protective immunity against a viral infection. In Example 9, Felgner describes injecting HIV-infected mice with a liposome formulation containing RNA encoding the HIV *nef* protein, and assaying the anti-viral effect of blood samples obtained from the treated mice. While Example 9 states that mice can be treated with *nef* RNA, and then subsequently challenged with the HIV virus, there is no actual data showing that such treatment can effectively protect mice from a subsequent HIV infection. In fact, according to Felgner (at page 57, lines 24-25), "... these results indicate a moderate anti-viral effect of the (*in vivo*) treatment (*emphasis added*)." Thus, aside from the fact that Felgner uses RNA, not DNA, there is no suggestion here that administration of nucleic acids encoding a viral protein can confer protective immunity against a subsequent viral infection. In other words, Felgner describes the partial effectiveness of its methods for treating an existing HIV infection, but no data whatsoever to show that the methods can work to vaccinate a subject prior to infection, to provide protective immunity against a later infection.

Similarly, in Example 19, although Felgner discloses that antibodies against gb-120 were detected in the blood of mice injected with a construct encoding gp-120, there is no data to show that the construct can protect these mice from an HIV infection that begins after immunization. Felgner merely concludes (at page 70, lines 34-36): "The study indicates that the gene retains its signal sequence, and the protein is efficiently excreted from cells." There is simply no suggestion here that administration of such a DNA construct as a vaccine can protect the subject

from a subsequent HIV infection. The Office has not pointed to any evidence to show that skilled practitioners would have expected a prophylactic DNA vaccine to be successful based on the disclosure of Felgner. Thus, not only does Felgner fail to disclose DNA vaccine against an influenza virus or a rotavirus, reading the reference, skilled practitioners also would not have expected a DNA vaccine to successfully immunize a subject against viral infection.

Huylebroeck does not remedy the deficiencies of Felgner. This reference discloses plasmid vectors for transient expression of DNA in animal cells (see, e.g., Abstract), and using these vectors to express influenza hemagglutinin HA in cultured cells (see, e.g., at page 173, right column). According to Huylebroeck (at page 179, right column, second paragraph), these vectors are useful tools because "... [transient] expression is a valuable and rapid system for investigating polypeptide regions responsible for various properties of viral antigens, in particular the immunogenicity, receptor-binding, enzymatic or fusogenic activities of membrane-bound glycoproteins ... (emphasis added)." There is nothing here that would have lead skilled practitioners to use these vectors to immunize vertebrates against later influenza infections.

This concept of using expression vectors as tools to study polypeptides expressed *in vitro* differs markedly from the concept of administering DNA directly to a subject for expression *in vivo* for immunizing the subject. As Huylebroeck does not even suggest the concept of DNA vaccines, it provides no further information regarding DNA vaccination to supplement the disclosure of Felgner. Accordingly, even assuming that skilled practitioners would have combined the teachings of Felgner and Huylebroeck, skilled practitioners would not have had an expectation that a vector encoding a viral antigen could be used successfully as a vaccine that protects against a subsequent challenge. Thus, the instant claims would not have been obvious over Felgner and Huylebroeck, individually or combined.

The Office also cites Townsend, but this reference similarly fails to rectify the deficiencies of Felgner and Huylebroeck. Townsend (at page 13, right column, the first full paragraph) used established cell lines expressing individual influenza genes "... to compare the roles played by the nucleoprotein and hemagglutinin molecules in target cell recognition by influenza A specific cytotoxic T cells." Like Huylebroeck, using transfected cells to study viral

proteins *in vitro* does not provide any suggestion for a DNA vaccine that provides a protective immune response. The Office (at page 10) cites Townsend for disclosing plasmids encoding hemagglutinins and routine isolation of influenza genes. However, the mere ability to construct a plasmid expressing an influenza gene is not the same as the ability to use the plasmid as an effective DNA vaccine against subsequent influenza infections.

The Office (at page 10) further points to Townsend for suggesting a vaccine that presents nucleoprotein in an appropriate form. While Townsend does make such a suggestion, it does so in the context of a discussion on whether cytotoxic T cells can also recognize denatured peptides presented on the cell surface, and not only viral antigens in their native conformation (see page 22, right column, the first two paragraphs). Applicants fail to see how this disclosure would have led skilled practitioners to any DNA vaccine, much less the expectation that a DNA vaccine would successfully immunize a vertebrate. In view of the foregoing, Townsend would not have led skilled practitioners to a method for immunizing a subject by direct administration of DNA to the subject. Furthermore, like Felgner and Huylebroeck, Townsend also fails to provide a reason for skilled practitioner to reasonably expect that such a method would have been successful. Accordingly, these three references, individually or combined, do not render the instant claims obvious.

Nor does Atkinson remedy these deficiencies of Felgner, Huylebroeck, and Townsend. The Office (at page 12 of the Office Action) is correct that Atkinson discloses plasmids encoding the rotavirus antigen VP7, but applicants have canceled all reference to rotavirus in the present claims, thus this reference has no further relevance to the present rejections.

The Office further cites (at pages 10-11) Andrianov for teaching using polymer encapsulated antigen to form a vaccine and using the polymer to deliver nucleic acid encoding an antigen to cells. Applicants have removed all reference to encapsulation in the present claims. Thus, this reference has not further relevance to the present rejections.

In view of the above, even assuming that skilled practitioners would have been led to combine the teachings of all of the cited references, they would not have had any expectation, much less a reasonable expectation, that direct administration of DNA encoding an influenza

viral antigen to a subject, prior to an infection of that subject by an influenza virus, could successfully immunize the subject against a subsequent viral infection. Thus, the instant claims would not have been obvious. Applicants respectfully request that this rejection be reconsidered and withdrawn.

## CONCLUSION

Applicants respectfully request that all claims be allowed. Applicants do not concede any positions of the Examiner that are not expressed above, nor do applicants concede that there are not other good reasons for patentability of the presented claims or other claims. The $555 fee for a three-month extension is being paid concurrently herewith on the Electronic Filing System (EFS) by way of Deposit Account authorization. Please apply any other charges or credits to deposit account 06-1050, referencing Attorney Docket No. 07917-217002.

Respectfully submitted,

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